(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization

International Bureau



I (BERTA BUNDADA) KERENTA MAN BERTA BURTA BURTA KUN 1 KERENTERBURTA BURTA BURTA BURTA BURTA BURTA BURTA BURTA B

(43) International Publication Date 9 October 2003 (09.10.2003)

PCT

(10) International Publication Number WO 2003/082834 A3

(51) International Patent Classification⁷: C07D 265/30, C07C 229/60, 215/18, A61K 31/5375, A61P 29/00

(21) International Application Number:

PCT/EP2003/003338

(22) International Filing Date: 27 March 2003 (27.03.2003)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data: 0207447.4

28 March 2002 (28.03.2002) GB

(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): ANCLIFF, Rachael, Ann [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). COOK, Caroline, Mary [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). ELDRED, Colin, David [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). GORE, Paul, Martin [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). HARRISON, Lee, Andrew [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). HAYES, Martin, Alistair [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). HODGSON, Simon, Teanby [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). JUDD, Duncan, Bruce [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). KEELING, Suzanne, Elaine [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). LEWELL, Xiao, Qing [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). MILLS, Gail [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). ROBERTSON, Graeme, Michael [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). SWANSON, Stephen [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). WALKER, Andrew, John [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). WILKINSON, Mark [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

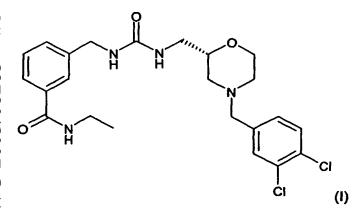
- (74) Agent: GIDDINGS, Peter, John; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report

[Continued on next page]

(54) Title: MORPHOLINE DERIVATIVES AND INTERMEDIATES THEREFOR



(57) Abstract: Compound of formula (I); which is;3-({[({[(2S)-4-(3,4-dichloroben-zyl)morpholin-2-yl]methyl}amino)carbonyl]--amino}methyl)-N-ethylbenzamide;and salts and solvates thereof, a process for its preparation, pharmaceutical formulations containing it and its use in therapy.



(88) Date of publication of the international search report: 25 March 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D265/30 C07C229/60 A61K31/5375 A61P29/00 CO7C215/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) $IPC\ 7\ C07D$

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

	ENTS CONSIDERED TO BE RELEVANT	olariant passages	Relevant to claim No.	
Category °	Citation of document, with indication, where appropriate, of the r	elevant passages		
4	WO 98 56771 A (SCHERING AG) 17 December 1998 (1998-12-17) cited in the application claims 1,31-34	1,3-5		
(SARTORI E ET AL: "SYNTHESIS AND ACTIVITIES OF NET ARYLSULFONAMING THROMBOXANE A2 RECEPTOR ANTAGON: EUROPEAN JOURNAL OF MEDICINAL CONTINENT OF SECURITY	9		
X Fur	ther documents are listed in the continuation of box C.	X Pätent family members are	listed in annex.	
'A' docum consi 'E' earlier filing 'L' docum which citation 'O' docum other	ategories of cited documents: nent defining the general state of the art which is not idered to be of particular relevance document but published on or after the international date ent which may throw doubts on priority claim(s) or his cited to establish the publication date of another on or other special reason (as specified) ment referring to an oral disclosure, use, exhibition or means ment published prior to the international filling date but .	"T" later document published after the or priority date and not in conflicited to understand the principle invention. "X" document of particular relevance cannot be considered novel or clinvolve an inventive step when to document of particular relevance cannot be considered to involve document is combined with one ments, such combination being in the art. "&" document member of the same priorities of the control of the same priorities."	t with the application but or theory underlying the ; the claimed invention cannot be considered to the document is taken alone ; the claimed invention an inventive step when the or more other such docu-obvious to a person skilled	
Date of the actual completion of the international search		Date of mailing of the internation	of mailing of the international search report	
(6 October 2003	15/10/2003		
Name and	I mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Hass, C		



PCT/EP 03/03338

C.(Continua	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category ^a	Citation of document, with Indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 31431 A (NISSHIN FLOUR MILLING CO; KIKUCHI HARUHIKO (JP); SATOH HIROAKI (JP) 23 November 1995 (1995-11-23) page 28, line 21 - line 24 page 35, line 20 - line 23 page 41, line 5	1,2,6-8, 10
A	EP 0 243 959 A (DAINIPPON PHARMACEUTICAL CO) 4 November 1987 (1987-11-04) page 43, example 24	1,10
A	WO 95 31442 A (NISSHIN FLOUR MILLING CO; KIKUCHI HARUHIKO (JP); SATOH HIROAKI (JP) 23 November 1995 (1995-11-23) page 40, line 6 - line 10 page 42, line 2 - line 4 page 43, line 5	10-12
A,P	WO 02 26723 A (HARRISON LEE ANDREW; JUDD DUNCAN BRUCE (GB); GLAXO GROUP LTD (GB);) 4 April 2002 (2002-04-04) claims 1,11,12,14,17-23,25,26; examples	1-8,10



INTERNATIONAL SEARCH REPORT

interponal application No. PCT/EP 03/0338

Box I	Observations where certain claims wer found unsearchable (Continuation of it m 1 of first sheet)
This Inte	emational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
	Although claim 4 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
• .5i. <u>· · ·</u>	"Cláims Nds:: " because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inte	ernational Searching Authority found multiple Inventions in this International application, as follows:
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
r 3. [·	As only some of the required additional search fees were timely paid by the applicant, this international Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. 🔲	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark	The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9856771	Α	17-12-1998	US AT	6207665 B1 232522 T	27-03-2001 15-02-2003
			AÜ	735462 B2	12-07-2001
		,	AU	8625898 A	30-12-1998
			DĒ	69811363 D1	20-03-2003
			DK	988292 T3	22-04-2003
			EE	9900565 A	15-06-2000
			EE	200200682 A	15-04-2003
			EE EE	200200683 A 200200684 A	15-04-2003 15-04-2003
			WO≈∴	200200084 A 9856771 A2	17~12~1 9 28~
			EP	1254899 A2	06-11-2002
			ĒΡ	0988292 A2	29-03-2000
			ĒS	2191320 T3	01-09-2003
			HU	0003929 A2	28-05-2001
			JР	2002503239 T	29-01-2002
			NO	996068 A	11-02-2000
			NO	20031373 A	11-02-2000
			PL	337758 A1	11-09-2000
			SK	171399 A3	12-09-2000
			TR US	9903034 T2 2003158205 A1	21-06-2000 21-08-2003
			US	2003130205 A1 2003139425 A1	24-07-2003
			US	6541476 B1	01-04-2003
			US	6534509 B1	18-03-2003
			ÜS	6573266 B1	03-06-2003
			US	2002177598 A1	28-11-2002
WO 9531431	Α	23-11-1995	BR	9507892 A	18-11-1997
			CA	2189964 A1	23-11-1995
			DE	69527786 D1	19-09-2002
			DE Ep	69527786 T2 0760362 A1	10-04-2003 05-03-1997
			WO	9531431 A1	23-11-1995
			US	5753654 A	19-05-1998
EP 0243959		04-11-1987	AT	79616 T	15-09-1992
2, 02,000		5 , 22 25 5.	AU	592177 B2	04-01-1990
			AU	7227587 A	05-11-1987
			CA	1291135 C	22-10-1991
			CZ	8702897 A3	11-11-1998
			DD	8702897 A3 256325 A5	04-05-1988
			DD DE	8702897 A3 256325 A5 3781195 D1	04-05-1988 24-09-1992
			DD DE DE	8702897 A3 256325 A5 3781195 D1 3781195 T2	04-05-1988 24-09-1992 18-02-1993
			DD DE DE DK	8702897 A3 256325 A5 3781195 D1 3781195 T2 218787 A	04-05-1988 24-09-1992 18-02-1993 31-10-1987
			DD DE DE DK EP	8702897 A3 256325 A5 3781195 D1 3781195 T2 218787 A 0243959 A1	04-05-1988 24-09-1992 18-02-1993 31-10-1987 04-11-1987
			DD DE DE DK EP ES	8702897 A3 256325 A5 3781195 D1 3781195 T2 218787 A 0243959 A1 2043617 T3	04-05-1988 24-09-1992 18-02-1993 31-10-1987
			DD DE DE DK EP ES FI	8702897 A3 256325 A5 3781195 D1 3781195 T2 218787 A 0243959 A1	04-05-1988 24-09-1992 18-02-1993 31-10-1987 04-11-1987 01-01-1994
			DD DE DE DK EP ES	8702897 A3 256325 A5 3781195 D1 3781195 T2 218787 A 0243959 A1 2043617 T3 871828 A ,B, 3005934 T3 18194 A	04-05-1988 24-09-1992 18-02-1993 31-10-1987 04-11-1987 01-01-1994 31-10-1987 07-06-1993 11-03-1994
			DD DE DK EP ES FI GR HU	8702897 A3 256325 A5 3781195 D1 3781195 T2 218787 A 0243959 A1 2043617 T3 871828 A ,B, 3005934 T3 18194 A 45514 A2	04-05-1988 24-09-1992 18-02-1993 31-10-1987 04-11-1987 01-01-1994 31-10-1987 07-06-1993 11-03-1994 28-07-1988
			DD DE DK EP ES FR HU HU	8702897 A3 256325 A5 3781195 D1 3781195 T2 218787 A 0243959 A1 2043617 T3 871828 A ,B, 3005934 T3 18194 A 45514 A2 198193 B	04-05-1988 24-09-1992 18-02-1993 31-10-1987 04-11-1987 01-01-1994 31-10-1987 07-06-1993 11-03-1994 28-07-1988 28-08-1989
			DD DE DK EP ES FR HU HU JP	8702897 A3 256325 A5 3781195 D1 3781195 T2 218787 A 0243959 A1 2043617 T3 871828 A ,B, 3005934 T3 18194 A 45514 A2 198193 B 1686407 C	04-05-1988 24-09-1992 18-02-1993 31-10-1987 04-11-1987 01-01-1994 31-10-1987 07-06-1993 11-03-1994 28-07-1988 28-08-1989 11-08-1992
			DD DE DK EP FI GK HU JP JP	8702897 A3 256325 A5 3781195 D1 3781195 T2 218787 A 0243959 A1 2043617 T3 871828 A ,B, 3005934 T3 18194 A 45514 A2 198193 B 1686407 C 3054937 B	04-05-1988 24-09-1992 18-02-1993 31-10-1987 04-11-1987 01-01-1994 31-10-1987 07-06-1993 11-03-1994 28-07-1988 28-08-1989 11-08-1992 21-08-1991
			DD DE DE ESI GK HU JP JP JP	8702897 A3 256325 A5 3781195 D1 3781195 T2 218787 A 0243959 A1 2043617 T3 871828 A ,B, 3005934 T3 18194 A 45514 A2 198193 B 1686407 C 3054937 B 63264467 A	04-05-1988 24-09-1992 18-02-1993 31-10-1987 04-11-1987 01-01-1994 31-10-1987 07-06-1993 11-03-1994 28-07-1988 28-08-1989 11-08-1992 21-08-1991 01-11-1988
			DD DE DK EP FI GK HU JP JP	8702897 A3 256325 A5 3781195 D1 3781195 T2 218787 A 0243959 A1 2043617 T3 871828 A ,B, 3005934 T3 18194 A 45514 A2 198193 B 1686407 C 3054937 B	04-05-1988 24-09-1992 18-02-1993 31-10-1987 04-11-1987 01-01-1994 31-10-1987 07-06-1993 11-03-1994 28-07-1988 28-08-1989 11-08-1992 21-08-1991

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
EP 0243959	A		PH SG SK SU US ZA KR	24049 A 494 G 289787 A3 1597101 A3 4870074 A 8703022 A 9508530 B1	05-03-1990 15-04-1994 03-06-1998 30-09-1990 26-09-1989 20-10-1987 31-07-1995
WO 9531442	Α	23-11-1995	BR CA DE DE EP ES WO US	9507666 A 2189963 A1 59513086 D4 69511086 T2 0760368 A1 2136291 T3 9531442 A1 5736550 A	23-09-1997 23-11-1995 92-09-1999 05-01-2000 05-03-1997 16-11-1999 23-11-1995 07-04-1998
WO 0226723	A	04-04-2002	AU BR CA CZ EP WO NO	9014601 A 0114321 A 2423305 A1 20031194 A3 1324991 A1 0226723 A1 20031443 A	08-04-2002 01-07-2003 04-04-2002 13-08-2003 09-07-2003 04-04-2002 26-05-2003